Drugs 1999 Feb; 57 (2): 225-230
0012-6667/99/0002-0225/$06.00/0

Sibrafiban

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Contents

Abstract

▲ Sibrafiban is the orally administered, nonpeptide, double-prodrug of Ro 44-3888 which is a selective glycoprotein IIb/IIIa receptor antagonist. It is currently undergoing clinical trials for secondary prevention of cardiac events in patients stabilised after acute coronary syndromes.

▲ In a phase II dose-finding study (TIMI 12) in patients stabilised after a myocardial infarction (MI) or an episode of unstable angina, there was a dose-dependent inhibition of platelet aggregation which correlated closely with the plasma concentration of the total active drug.

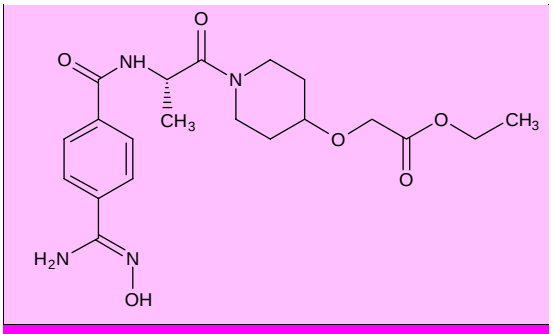
▲ An ongoing phase III study (SYMPHONY) compares the effects of sibrafiban on cardiac events with that of aspirin in patients stabilised after a Q wave MI or an episode of unstable angina.

▲ This large trial uses twice daily dosage regimens to produce the plasma concentrations which were associated with less bleeding in the earlier dose-ranging trial.

▲ A long term (minimum duration 12 months) phase III study (2nd SYMPHONY) is under way to compare the effects of sibrafiban on cardiac events with those of aspirin in patients stabilised after an MI or an episode of unstable angina.

▲ The most common adverse events associated with sibrafiban include bleeding, with minor haemorrhages occurring more often than with aspirin.

Features and properties of sibrafiban (Ro 48-3657)	
Indications	
Secondary prevention of acute coronary syndromes	Late phase clinical trials
Mechanism of action	
Platelet aggregation inhibitor	Double-prodrug of the active compound Ro 44-3888 which is a selective glycoprotein IIb/IIIa receptor antagonist
Dosage and administration	
Usual dose in clinical trials	3 to 6mg
Route of administration	Oral
Frequency of administration	Twice daily
Pharmacokinetic profile (of Ro 44-3888)	
Peak plasma concentration	22 to 64 μg/L (after multiple doses of 3 to 10mg twice daily) 35 to 65 μg/L (after multiple doses of 5 to 15mg once daily)
Time to peak plasma concentration	6h
Elimination half-life	11h
Adverse events	
Most frequent	Minor haemorrhage, most commonly epistaxis, gastrointestinal haemorrhage, bleeding gums
Serious events	Major haemorrhage



Sibrafiban

Sibrafiban is the orally active, nonpeptide, double-prodrug of Ro 44-3888, a selective antagonist of the glycoprotein (GP) IIb/IIIa platelet receptor. A double-prodrug is an agent which is first metabolised to the prodrug and then to the active compound.[1]

Agonists such as adenosine diphosphate (ADP), collagen, epinephrine (adrenaline), thromboxane A_2, platelet activating factor, serotonin and thrombin play a role in the activation of the GP IIb/IIIa receptor, the final common pathway of platelet aggregation. The activated receptor binds fibrinogen and von Willebrand factor which facilitates platelet aggregation and thrombus formation.[2-4]

Antiplatelet agents such as sibrafiban are expected to be beneficial in reducing platelet-mediated ischaemic events in patients with acute coronary syndromes.

In this review, acute coronary syndromes are defined as unstable angina, non-Q wave myocardial infarction (MI) or Q wave (acute) MI.[5]

1. Pharmacodynamic Profile

Animal Studies

- The effects of Ro 44-3888 on the platelet aggregation response to ADP (17 μmol) and on cutaneous bleeding times was determined in 8 rhesus monkeys given sibrafiban 0.25 or 0.5 mg/kg/day orally for 8 days. The maximum inhibition of *ex vivo* platelet aggregation and prolongation of bleeding time by Ro 44-3888 were dose dependent. Peak effect on platelet aggregation was achieved 3 hours after the dose and returned to predose levels after 24 to 36 hours: platelet aggregation was 28 and 4% of the predose response at 3 hours after the 0.25 and 0.5 mg/kg doses, respectively (data extrapolated from graph).[6]

- Bleeding times increased from 1 minute immediately before both doses to 11 and 23 minutes 3 hours after the 0.25 and 0.5 mg/kg doses, respectively. A decrease, almost to predose values (2 minutes), was observed after 24 to 36 hours (data extrapolated from graph).[6]

- In another *ex vivo* study in beagles, the effect of oral sibrafiban (20 mg/kg) [duration of treatment not provided] on ADP-induced platelet aggregation was not altered by the coadministration of either heparin and aspirin or heparin and recombinant tissue-type plasminogen activator (rt-PA) [doses not provided]. Buccal mucosa bleeding time was prolonged 4- to 5-fold by the addition of heparin and aspirin but did not differ significantly from that observed after sibrafiban alone. Bleeding time increased for the duration of the rt-PA infusion after coadministration with sibrafiban (further data not provided).[7]

Human Studies

The information in this section has been obtained from the phase II, dose-ranging TIMI 12 (Thrombolysis in Myocardial Infarction) trial (see section 3 for study details).[8]

- *Ex vivo* inhibition of ADP (20 μmol/L)-induced platelet aggregation was linear to the dose and correlated with the maximum plasma concentration of the total active drug in 103 patients stabilised after a non-Q wave or Q wave MI, or an episode of unstable angina who received oral sibrafiban (3, 5, 7 or 10mg twice daily or 5, 10 or 15mg once daily for 28 days) (fig. 1). The degree of inhibition of ADP-induced platelet aggregation was sustained for longer with twice than once daily regimens: 40 and 70% inhibition was still apparent 24 hours after the 5 and 10mg twice daily doses, respectively, but

platelet function had returned to baseline 24 hours after once daily doses.[8]

• Similarly, steady-state Ivy bleeding time (measured at trough) increased with increasing dose.[8]

• Mean peak inhibition of ADP-induced platelet aggregation on day 28 (steady state) ranged from approximately 43 to 93% after sibrafiban 3, 5, 7 and 10mg twice daily and approximately 59 to 93% after sibrafiban 5, 10 and 15mg once daily (data extrapolated from graph) [fig. 1].[8]

• The mean IC_{50} of active drug (plasma concentration of Ro 44-3888 causing 50% inhibition of platelet aggregation) was 15 μg/L and did not differ significantly on days 1 and 28 (13.8 *vs* 15.9 μg/L, n = 76).[8]

• TRAP (thrombin receptor activation peptide)-induced platelet inhibition also showed a linear correlation to dose and inhibition was sustained for longer with twice than with once daily dosage regimens.[8]

2. Pharmacokinetic Profile

• Oral sibrafiban (3, 5, 7 or 10mg twice daily or 5, 10 or 15mg once daily for 28 days) resulted in dose-dependent increases in the maximum plasma concentration (C_{max}) of Ro 44-3888 in 103 patients stabilised after an MI or an episode of unstable angina.[8]

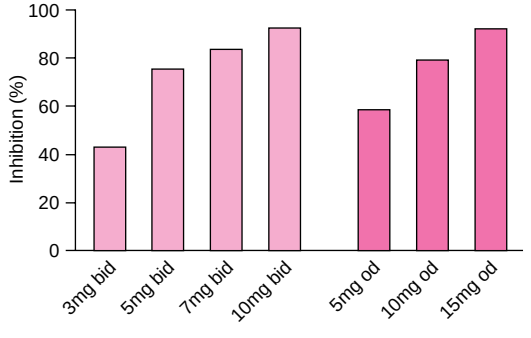


Fig. 1. Effects of oral sibrafiban on platelet aggregation. Mean peak inhibition of adenosine diphosphate (ADP)-induced platelet aggregation after 7 different dosage regimens of sibrafiban given orally for 28 days in 103 patients with Q wave or non-Q wave myocardial infarction, or unstable angina (values extrapolated from graph).[6] **bid** = twice daily; **od** = once daily.

• C_{max} values ranged from 20 to 45 μg/L on day 1 and 22 to 64 μg/L on day 28 after the twice daily regimens. Corresponding values for the once daily regimens were similar: 23 to 55 μg/L on day 1 and 35 to 65 μg/L on day 28. The mean trough to peak concentration ratio of Ro 44-3888 after twice daily dosage regimens was 45%. The time to reach C_{max} after all doses was approximately 6 hours.[8]

• The elimination half-life of Ro 44-3888 was 11 hours.[8]

• After a single intravenous infusion of Ro 44-3888 (0.2 mg/kg over 90 minutes) to rhesus monkeys, the volume of distribution at steady state was 0.8 L/kg.[6]

3. Therapeutic Trials

TIMI 12

• The main aims of the phase II, dose-ranging, double-blind, multicentre TIMI 12 were to examine pharmacokinetic and pharmacodynamic parameters, safety and tolerability after various dosages of sibrafiban. The effects of sibrafiban on cardiac events were also included, although this study was not powered to detect differences in clinical events between treatment groups. The results of this trial allowed sibrafiban dosages to be better titrated in the ongoing phase III SYMPHONY and 2nd SYMPHONY trials.

• 323 patients stabilised after a non-Q wave MI, Q wave MI or unstable angina were given oral sibrafiban 5, 7 or 10mg twice daily, sibrafiban 15mg once daily or aspirin 160mg once daily (B. Steiner, personal communication) for 28 days. The use of concomitant heparin, but not thrombolytic therapy or warfarin, was permitted during the study and other medication was allowed at the physician's discretion (no further details provided).[8]

• In a randomised cohort of 220 patients, the incidence of cardiac events (death, MI or recurrent ischaemia) did not differ significantly between

treatment groups [4, 5.4 or 3.8% (2 patients in each group) after sibrafiban 5, 7 or 10mg twice daily, respectively, 10.3% (3) after sibrafiban 15mg once daily and 3.8% (2) after aspirin]. A similar result was observed in the remaining 103 patients who had participated in a pharmacokinetic/pharmacodynamic study (details not provided). However, as mentioned earlier, the study was not adequately powered to detect a difference.[8]

- During the 14 days after the end of treatment (to day 42) the incidence of cardiac events increased in patients receiving sibrafiban 5 or 10mg twice daily (to 6 and 7.7%; 3 and 4 patients, respectively) and in sibrafiban 15mg once daily recipients (to 13.8%; 4 patients) but no further events were observed in the other treatment groups.[8]

- No patients died while receiving treatment with either agent, but 2, 1.9 and 3.4% (1 for each group) of patients initially receiving sibrafiban 5 or 10mg twice daily or sibrafiban 15mg once daily died during the period after treatment. An MI was experienced by 2% (1) and 3.4% (1) of patients receiving sibrafiban 5mg twice daily and sibrafiban 15mg once daily but was more frequent during the 14 days after treatment only in sibrafiban 10mg twice daily recipients (from 0 to 1.9%; 1).[8]

- The incidence of recurrent ischaemia remained the same during the whole assessment period: 2, 5.4, 3.8 or 6.9% (1 or 2) of patients receiving sibrafiban 5, 7 and 10mg twice daily or 15mg once daily, respectively, and 3.8% (2) of aspirin recipients.[8]

The SYMPHONY Trial

- The phase III, randomised, double-blind, multicentre SYMPHONY (The Sibrafiban Versus Aspirin to Yield Maximum Protection from Ischaemic Heart Events Post Acute Coronary Syndromes) trial[1] uses twice daily dosage regimens of sibrafiban, which were associated with lower bleeding rates in TIMI 12. The dosages of sibrafiban were chosen to achieve plasma Ro 44-3888 levels of between 7 and 40 μg/L as determined by TIMI 12.

- Dosages were individualised for each patient, according to renal function and bodyweight, in order to reduce interpatient variability in the plasma concentration of sibrafiban and the degree of platelet inhibition, and to reduce bleeding risk.[1]

- This study recruited about 9000 patients stabilised after a Q wave MI or an episode of unstable angina and compares the efficacy of 90 days of sibrafiban [3, 4.5 or 6mg twice daily (upper end of the plasma concentration range) or 3 or 4.5mg twice daily (lower end of the plasma concentration range)] with that of aspirin (80mg twice daily). The long term efficacy of treatment will be evaluated at 6 and 12 months.[1]

- Clinical end-points include death from any cause, MI or reinfarction and severe recurrent ischaemia at 90 days and at 6 and 12 months, and the incidence of reversible myocardial ischaemia, stroke, coronary revascularisation and rehospitalisation at 90 days. In addition, the comparative tolerability profiles of sibrafiban and aspirin will be assessed and pharmacoeconomic data collected.[1]

The 2nd SYMPHONY Trial

- A long term phase III trial is under way and will recruit about 8400 patients after a non-Q wave or Q wave MI or an episode of unstable angina.[9]

- This double-blind, randomised trial will compare the efficacy, safety and tolerability of 1 to 2 years' (minimum duration 12 months) treatment with sibrafiban 3, 4.5 or 6mg twice daily (higher end of plasma concentration range) or 3 or 4.5mg twice daily (lower end of plasma concentration range) with that of aspirin (80mg twice daily). As in SYMPHONY, sibrafiban doses will be individualised according to patients' renal function and bodyweight, but, unlike in SYMPHONY, the lower concentration arm will be combined with aspirin (80mg twice daily).[9]

- Efficacy end-points include the individual or combined incidence of death from any cause, MI or reinfarction, severe recurrent or reversible coronary ischaemia, coronary revascularisation, stroke and rehospitalisation. Safety and tolerability end-

points and pharmacoeconomic issues will also be assessed.[9]

4. Tolerability

The information presented in this section has been obtained from a dose-ranging study (TIMI 12) comparing aspirin with various once or twice daily dosage regimens of oral sibrafiban in 323 patients with MI or unstable angina (see section 3 for further details).[8] Because of the increased incidence of bleeding associated with once daily administration, this dosage regimen has been abandoned. Twice daily dosage schedules will be used in future clinical trials for reasons outlined in section 3.

- A major haemorrhage occurred only with the 7mg twice daily and 15mg once daily dosages and was reported by 3 and 4% of patients, respectively. A minor haemorrhage occurred in 17.1% of 271 sibrafiban recipients (range 0 to 21% after 3 to 10mg twice daily and 20 to 32% after 5 to 15mg once daily) [fig. 2].[8]
- Haemorrhaging resulted in the discontinuation of treatment by 0 to 13% of patients after sibrafiban 3 to 10mg twice daily and by 0 to 32% of patients after 5 to 15mg once daily. In comparison, aspirin 160mg daily (B. Steiner, personal communication) resulted in major and minor haemorrhages in 2 and 0% of 52 recipients, respectively, (fig. 2) with 2% of patients discontinuing treatment.[8]
- The most common types of primary bleeding in patients receiving sibrafiban were epistaxis (6.3%), gastrointestinal haemorrhage (2.2%) and bleeding gums (1.8%). An average of 4.4% (range 0 to 11%) of sibrafiban recipients needed medical intervention (e.g. nasal packing) for bleeding and 3.4% (range 0 to 6%) needed a blood transfusion. Medical intervention was not needed by any aspirin recipients but 2% underwent a transfusion. One sibrafiban recipient developed thrombocytopenia which normalised after treatment was stopped.[8]
- The risk of minor bleeding was associated with the total daily dose of sibrafiban, and with once daily compared with twice daily dosage regimens (fig. 2), thus correlating with the higher maximum plasma concentrations achieved with these dosage schedules. Furthermore, the rate of haemorrhaging was higher in patients with unstable angina than with an MI, and in patients with a calculated creatinine clearance of <4 L/h.[8]

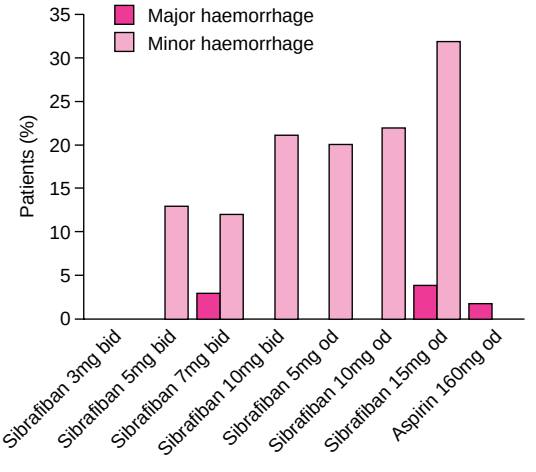


Fig. 2. Effects of oral sibrafiban on bleeding rates. Incidence of major and minor haemorrhages occurring in 323 patients with non-Q wave or Q wave myocardial infarction or unstable angina after 7 different dosage regimens of oral sibrafiban or after aspirin for 28 days.[6] **bid** = twice daily; **od** = once daily.

5. Sibrafiban: Current Status

Sibrafiban, the orally administered double-prodrug of the nonpeptide GP IIb/IIIa receptor antagonist Ro 44-3888, is currently in late phase clinical trials worldwide for the secondary prevention of cardiac events in patients with acute coronary syndromes. The rate of major haemorrhages is similar to that of aspirin but the incidence of minor haemorrhages at dosages currently studied was higher.

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